REMARKS

Claims 103-132 are pending in the application. Claims 103, 109, 115, 116, 118, 124, 125, and 127 are amended. Accompanying this response is a Declaration under CFR 1.132 by inventor Dave S.B. Hoon.

Drawings

Drawings have been amended in accordance with the requirements of the Office by properly numbering multiple views. Replacement sheets 1/8 - 8/8 of drawings are enclosed.

Interview Summary

An in-person interview was conducted on March 30, 2011 between undersigned and Examiner Pohnert. Applicants thank the Examiner for his time and consideration in the interview. The Examiner suggested that limiting the control DNA to human DNA should allow for withdraw of part of the enablement rejection. The Examiner further agreed that a demonstration in the prior art of circulating acellular DNA in normal individuals may overcome part of the enablement rejection. The Examiner suggested that demonstration that the markers are predictive of response to other claimed therapies may overcome part of the enablement rejection. There was also discussion about written description relative to claims 118 and 127. There was an agreement that a specific recitation in the independent claims that a comparison between a subject having a loss of heterozygosity (LOH) at one or more of the DNA markers and a subject with no LOH at the DNA markers would overcome the indefiniteness rejection. The Examiner agreed that a more thorough declaration by Dr. Hoon following the logic presented by the

representative or more data similar to the representative's opinion may allow for the withdrawing on the 103 rejection. No agreement on patentability was reached.

Rejections under 35 U.S.C. § 112

The pending claims are rejected under 35 U.S.C. § 112, 1st paragraph, because:

1) "the specification and prior art do not reasonably provide enablement for comparison to any control sample" (Office Action, p. 7) for claims 103 -132,
2) "[t]he specification teaches only the concurrent BC regimen of dacarbazine (DTIC), cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen" (Office Action, p. 15) which is the basis for both an enablement and written description rejection of claims 118 and 127,
3) the terms "lower probability of survival," "poor prognosis," predicting the cancer therapy efficacy of the subject having a loss of heterozygosity of one or more of the DNA markers will likely be poor," and "poor likelihood of responding" are relative terms which render the claims indefinite absent a recitation of what that the term is in relation to for claims 103 -132 (Office Action, pp. 21-22), and
4) "it would be unpredictable to detect responsiveness to any chemotherapy, radiation therapy, gene therapy, immunotherapy or surgical procedure as O'day et al. teaches different chemotherapy agents have different response rates for claims 116 and 125 (Office Action, p. 20).

Control DNA

The Office Action asserts that the term "control DNA" means "any control sample" regardless of species. To avoid any further issue over the scope of the term "control sample," the independent claims have been limited to recited a "control human DNA."

The Office Action states:

> In order to practice the invention as claimed one of skill in the art would first have to determine if it would be predictable to practice the invention relative to any control sample from any biological fluid or tissue from a "normal" subject. Thus [it] would be unpredictable as the specification teaches that LOH was not found in the blood of a "normal subject."
> Office Action p. 19.

At the time the present application was filed, it was well known in the art that aberrant acellular DNA was present in the blood of healthy individuals and individuals suffering from metastatic melanoma. Hoon Decl. ¶ 3, Fujiwara et al., Cancer Research, 1999, volume 59, p. 1567 (2nd column, last ¶), p. 1568 (1st column, 1st ¶), p. 1570 (2nd column, 1st ¶). Control DNA from a healthy individual or a normal cell would be diploid (two copies) for the marker, which one of skill in the art could readily compare to a subject's sample DNA which could either be diploid (two copies) or show a LOH (one copy). Hoon Decl. ¶ 4.

"The strategy of the present invention is to utilize genetic differences between normal and cancer cells for diagnosis and monitoring of melanoma patients." '956 Application p. 9, lines 3-4. Logically, that is all that is required to determine if a LOH has occurred, a simple comparison of a healthy sample to a diseased sample. The specification continues:

> Through the use of DNA probes, DNA from an individual's normal cells can be compared with DNA extracted from the same individual's tumor cells and LOH can be identified using experimental techniques well known in the art. Alternatively, LOH can be assayed by demonstrating two polymorphic forms of a protein in normal heterozygous cells, and only one form in cancer cells where the deletion of an allele has occurred.
> '956 Application p. 7, lines 10-15.

> According to the method of the present invention, DNA is isolated from a biological fluid of a patient. For comparison, a control DNA sample may be prepared, for example, from a non-neoplastic tissue from the same patient, **or from a**

biological fluid or tissue from a normal person.
'956 Application p. 14, lines 12-14 (emphasis added).

The specification enables a comparison of normal human DNA against a blood, serum or plasma sample from a metastatic melanoma patient. And, as explained above normal human DNA would have two copies of the marker.

At page 19, the Office Action states "the specification and prior art has provided no evidence that the a control DNA from urine, hair, feces, etc have the DNA marker at the diploid level so as to allow one of skill in the art to determine a LOH such as to practice the invention as claimed." Normal tissue, cells and DNA are diploid in nature for the identified markers including those found in urine, hair or feces. Hoon Decl. ¶ 4. Applicant note, however, that the claims do not recite urine, hair or feces.

Biochemotherapy and Responsiveness to Cancer Therapy

The Office Action asserts that the claims 116 and 125 are not enabled because they are not limited to biochemotherapy because "O'day et al teaches different chemotherapy agents have different response rates." Claims 118 and 127 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. To expedite prosecution, the claims 118 and 127 have been limited to the biochemotherapy regimen which is the combination of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

Biochemotherapy by definition is made up of immunotherapeutics and chemotherapeutics and the findings in the '956 Application relative to biochemotherapy would be expected to be readily applicable to both immunotherapeutics and chemotherapeutics. One of ordinary skill in the art would understand and accept that that our finding could be readily applied to any other treatment of metastatic melanoma (such

as chemotherapy, radiation therapy, immunotherapy, surgical procedure, and a combinations of those therapies) without undue experimentation because the microsatellite markers are not specific to biochemotherapy. Hoon Decl. ¶ 6.

Relative terms

Lastly, claims 103-132 are rejected as indefinite. The Office Action states that the term "lower probability of survival" in claim 103, the term "poor prognosis" in claim 109, the term "predicting the cancer therapy efficacy of the subject having a loss of heterozygosity of one or more of the DNA markers will likely be poor" in claim 115, and the term "poor likelihood of responding" in claim 124 are indefinite because the claims do not recite a comparison to which these terms relate. Claims 103, 109, 115 and 124 have been amended to recite that the relative terms are compared to "a subject with no loss of heterozygosity at the DNA markers" as suggested by the Office Action (page 7).

Rejections under 35 U.S.C. § 103(a)

Claims 103-132

In the Office Action, claims 103-132 are rejected under 35 U.S.C. § 103(a) as being not patentable over Soengas, et al. (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al. (Cancer Research (1999) volume 59, pages 1567-1571) because "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood, plasma, or serum as taught by Fujiwara, for detection of markers associated with melanoma progression because Fujiwara teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids." Office Action, p. 6. Applicants

respectfully disagree.

As the Office Action notes "Soengas does not teach the use of acellular DNA from plasma, serum, or blood as a sample." Office Action, p. 24. Fujiwara does not teach a method of detecting the presence of markers D12S1657, D12S393, D12S1706 and D12S346, but focuses on a different set of acellular markers to detect LOH in melanoma patients. Neither Soengas, Fujiwara, nor the combination of the two teach or suggest methods of predicting the probability of survival, the prognosis, or the efficacy of cancer therapy for metastatic melanoma patients by detecting the loss of heterozygosity at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346 in acellular DNA found in the blood, serum or plasma.

The focus of Soengas is Apaf-1 expression and LOH, not LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346. The only data disclosed in Soengas directed to LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346 is in Figures 1b & 1c at p. 207 where Soengas discloses the LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346 in metastatic melanoma tumors and associates the LOH with Apaf-1 expression as determined by measuring mRNA. Hoon Decl. ¶ 8. That is all Soengas discloses with respect to LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346.

Soengas does not teach or direct one of ordinary skill in the art to measure the LOH at microsatellite DNA markers D12S327, D12S1657, D12S393, D12S1706, and D12S346 from acellular DNA derived from the blood of a metastatic melanoma patient to predict the probability of survival, prognosis, or cancer therapy efficacy. Hoon Decl. ¶ 9.

Nevertheless, the Office Action concludes that '[t]he combination of Soengas and Fujiwara would have resulted in a method of detecting the presence or absence of D12S327, D12S1657, D12S393, D12S1706, and D12S346 markers in acellular DNA from blood, serum or plasma and from this detection allow prediction of probability of survival, prognosis, efficacy and response to therapy as Soengas teaches the loss is associated with a loss of response to chemotherapeutic agents and Fujiwara teaches increasing LOH results in poor prognosis and is associated with more advanced melanoma."

The Office Action is premised on two flawed assumptions. First, the observed LOH in a primary or metastatic tumor for a given set of markers, such as Soengas, can predict the therapeutic value of the LOH of the same markers in acellular DNA from blood, serum or plasma. Second, that the LOH in acellular DNA observed in Fujiwara necessarily translates into the present application's clinically relevant method claims. Both assumptions are incorrect.

Fujiwara examined the plasma of 76 melanoma patients and 20 healthy patients. Fujiwara, Materials and Methods, Specimens, p. 1568. Of those 76 melanoma patients, 57 had advanced staged melanoma (Stage III and Stage IV) and 19 had early staged melanoma (Stage I and Stage II). Fujiwara, p. 1567. Fujiwara analyzed the LOH for a panel of 10 microsatellite markers representing six chromosomal regions in both acellular DNA found in the blood and also DNA found in tumor cells from tumor biopsies. Fujiwara, pp. 1567-1568. Of the 76 patients, matched tumor biopsies and acellular DNA were examined in 40 patients. Fujiwara, Results, p. 1568. Consequently, Fujiwara demonstrated that, while LOH of microsatellite markers can be determined from acellular

DNA, the LOH of microsatellite markers from informative metastatic melanoma tumors and informative acellular DNA from metastatic melanoma patient was not identical or predictable. Hoon Decl. ¶¶ 9, 11.

Taback et al., Cancer Res., 2001, vol. 61, 5723-5726, examined eight microsatellite markers for LOH. Of the eight only two microsatellite markers (D1S228 and D9S157) had prognostic value (LOH of these makers was found to indicate a poor prognosis for survival. Taback noted that:

> D9S157 is isolated to chromosome 9p21-22, which is one of the most studied deletion regions in melanoma. It has been shown to occur in up to 60% of cases, and loss of this region has been linked to tumor suppressor gene CDKN2A that is involved in cell cycle arrest and other potential unidentified tumor suppressor gene(s). In one study, evaluating LOH in primary tumors for clinical correlation did not identify a prognostic value for this particular marker. Taback, p. 5726.

The finding that LOH at D9S157 in acellular DNA had prognostic value for survival was unexpected. That finding underscores the unpredictability of the prognostic value of LOH on microsatellite DNA markers in acellular DNA relative to LOH in primary tumor. Simply put, LOH in primary tumor does not predict the prognostic value of LOH on microsatellite DNA markers in acellular DNA. Hoon Decl. ¶16. Thus, the assumption that observed LOH in a primary or metastatic tumor for a given set of markers, such as Soengas, can predict the LOH in acellular DNA from blood, serum or plasma has been shown to be incorrect. The prognostic value of a LOH found in the primary or metastatic has been shown to be unpredictable when applied to LOH in acellular DNA found in the blood, serum or plasma. Thus, Soengas' findings for the microsatellite markers in tumors does not render the present claims directed to acellular DNA obvious because the prognostic value of tumor findings are not predictive of acellular DNA. Hoon Decl. ¶14.

Fujiwara analyzed the LOH for a panel of 10 microsatellite markers for their

correlation with clinical stage and known melanoma prognosis factors. Fujiwara found a significant correlation between the number of LOH microsatellite markers within a patient's plasma and the AJCC stage in the 76 patients. Fujiwara, Results, p. 1568. However, Fujiwara found that only one marker (D3S1293) out of ten, a marker which is not the marker recited in the present claims, was found to have a significant correlation between LOH detection and clinical progression of disease. Fujiwara, Results, p. 1568. For combinations of markers, three combinations (D9S157 & D3S1293, D9S157 & D1S228, and D11S925 & D3S1293), none of which are the recited in the present claims, were most significant in correlating progression of different clinical stages of disease. Notably, the teachings of Fujiwara are directed to the LOH and its association with disease progression. Fujiwara concludes that "[t]here was no significant correlation between the frequency of LOH in the plasma or tumor, and standard prognostic factors such as Breslow's thickness or Clark's level." Fujiwara, Results, p. 1568. 11. Two years after Fujiwara, it was noted in Taback et al., Cancer Res., 2001, vol. 61, 5723-5726 that "[t]o date, no major study in solid nonviral-related tumors has determined any significant clinical utility or prognostic value of these free-circulating DNA markers." Simply put, the prognostic value of LOH in microsatellite DNA markers in melanoma tumors cannot predict the prognostic value of LOH in the same microsatellite DNA markers in acellular DNA. Thus, the findings of Soengas and Fujiwara would not enable one of ordinary skill the art to predict the probability of survival, the prognosis, or the biochemotherapeutic efficacy of metastatic melanoma patients based upon the LOH of microsatellite markers in acellular DNA generally (Fujiwara), or the markers of the present claims specifically in tumors (Soengas). Hoon Decl. ¶¶ 9, 10, 13-15.

Claims 118 and 127

In the Office Action, claims 103-132 are rejected under 35 U.S.C. § 103(a) as being not patentable over Soengas, et al. (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al. (Cancer Research (1999) volume 59, pages 1567-1571) because:

> [i]t would be prima facie obvious to one of skill in the art at the time the invention was made to predict long term survival (efficacy of response) of stage IV melanoma to dacarbazine, vinblastin, cisplatin, decrescendo IL-2, interferon alpha-2b, IL-2, and tamoxifen in view of the teachings of Soengas and Fujiwara with a reasonable expectation of success. The teachings of Soengas suggest that the loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers results decreased apoptosis, which in turn results in increase chemoresistance to chemotherapeutic agents in melanoma. Thus, it would have been obvious to one of skill in the art that subjects with stage IV melanoma and LOH of markers known to be associated with decreased apoptosis in melanoma in response to a chemotherapeutic drug (adriamycin) would also be associated with decreased apoptosis and thus chemoresistance to other known chemotherapeutic agents.
> Office Action at p. 31.

The teachings of Soengas and Fujiwara are discussed at length above. The prognostic value of chemotherapy LOH in microsatellite DNA markers in melanoma *tumors* cannot predict the prognostic value for biochemotherapy of LOH in the same microsatellite DNA markers in *acellular DNA* as explained above. Thus, the findings of Soengas and Fujiwara would not enable one of ordinary skill the art to predict biochemotherapeutic efficacy of metastatic melanoma patients based upon the LOH of microsatellite markers in acellular DNA generally (Fujiwara), or the markers of the present claims specifically in tumors (Soengas).

CONCLUSION

In view of the foregoing, it is submitted that the claims are in condition for allowance. A Notice of Allowance is requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to contact the undersigned at 310-788-9900.

Respectfully submitted,

Perkins Coie LLP

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/ Michael J. WISE /
Michael J. Wise
Registration No. 34,047

Correspondence Address:
Customer No. 34055
Perkins Coie LLP
P.O. Box 1247
Seattle, Washington 98111-1247
(310) 788-9900